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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference H 28045PC Bö/sa	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/10333	International filing date (*day/month/year*) 22 December 1999 (22.12.99)	Priority date (*day/month/year*) 23 December 1998 (23.12.98)
International Patent Classification (IPC) or national classification and IPC G01N 33/58		
Applicant AVENTIS RESEARCH & TECHNOLOGIES GMBH & CO. KG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11 April 2000 (11.04.00)	24 November 2000 (24.11.2000)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP99/10333

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-13, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-36, filed with the letter of 31 October 2000 (31.10.2000),
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/5-5/5, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-36	YES
	Claims		NO
Inventive step (IS)	Claims	1-24	YES
	Claims	25-36	NO
Industrial applicability (IA)	Claims	1-36	YES
	Claims		NO

2. Citations and explanations

This report makes reference to the following documents:

D1 US-A-5 635 352
D2 WO-A-98/23956.

1. Due to the clarification that the "markers" are constituents of the sample to be analysed, the methods explained in independent Claims 1 and 2 are novel over test methods which involve the determination **of a single analyte** using multiple indirect detection (see D1 and Box VIII, item 4).

Moreover, the features as described in the claims cannot obviously follow from the prior art according to the search report.

The method according to Claims 1 to 24 appears to be novel and to involve an inventive step and thus to meet the requirements of PCT Article 33(2).

2. Claim 1 relates to test kits which contain (at least) two detection species for binding two different analytes ("markers") by complex formation, two of the binding species being marked in a

different manner.

Unlike Claims 1 and 2, the wording of the claim does not show the functional relationship between the different markers and detection species, e.g. whether complexes that are each separate (e1 x m1 or e2 x m2) are formed or a complex containing all of the constituents is formed.

Methods for simultaneous determination of a plurality of analytes using detection reagents which can be distinguished from each other and are specific to the respective analyte are known from the prior art (see D2, page 1, lines 25-28, page 2, lines 13-26 and page 4, lines 21-23). A person skilled in the art would consider it obvious to combine the necessary reagents, in particular the detection species in the form of a test kit. Such kits would be covered by the protective scope of the present broad Claims 25 and 26.

The claims mentioned thus do not meet the requirements of PCT Article 33(3) (see also Box VIII, item 5).

The objection relates similarly to dependent Claims 28, 32 and 33, whose features are already described in D2, and to Claims 34 to 36 concerning the conventional use of the obvious test system in known test methods (which according to the wording of the claim do not have to be the same as the methods mentioned in Claims 1 and 2).

3. The features of dependent Claims 27, 29 to 31 cannot be derived from D2. However, taking these features

into consideration in the generic claims does not result in a product that would be specially adapted to the embodiment of the method according to the invention, and might solve the predetermined statement of the problem.

The aforementioned claims thus do not satisfy the requirements of PCT Article 33(3) (see also Box VIII, item 6).

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. According to Claim 1 the substances to be analysed as assay components referred to as markers are, for example, in a clinical sample. As such "markers" or more accurately expressed "analytes" are **fundamentally in an unmarked form and unknown concentration**. However, the two working examples present are based on determining **a single unmarked** substance **to be considered as an analyte in this way**. The working examples are therefore not covered by the protective scope of the present claims. With respect to the reagents used (the substance referred to as "marker 2" was added as a fluorescein-marked derivative and in a predetermined concentration) the examples describe a method for determining **a single analyte** using multiple indirect marking.

Consequently, there is a contradiction between the experimental part of the description and the subject matter of the claim. The application thus does not meet the requirements of PCT Article 6.

Methods using multiple indirect marking and signal amplification are already described in D1. If the term "marker" were to be interpreted to mean that it comprises reagents added in a predetermined amount and marked in a particular manner, whose function would be described more accurately by the expression "detection species" there would be an objection because of the lack of novelty in relation to D1.

As described in the two present working examples,

VIII. Certain observations on the international application

the reagent referred to as "m2" is not an analyte but acts as a detection agent and can thus be understood to be a fourth detection species "e4" with respect to its signal function and localisation in the resulting reaction complex. Consequently, it has the same function as the label probe "LP" as shown in Figures 7, 8 and 12 in D1.

2. Unlike the method in Claim 1, in the method according to Claim 2 **without selecting specific marking groups and technologies** partial complexes that each contain only one of the (unmarked) analytes (and thus would not be assessed as being positive) cannot be distinguished from "complete" complexes of the conformation e1 x m1 x e2 x e3 x m2.

Consequently, Claim 2 does not seem to contain all the method features and adaptations required for successful reaction of the method, thereby not satisfying the requirements of PCT Article 6.

3. Unlike Claims 1 and 2, the kit Claims 25 and 26 do not include any specifications concerning the interrelationship of the detection species with the different marker substances. The test kits claimed accordingly are therefore not recognisably adapted specially for the methods according to the invention (see also Box V, items 2 and 3).

The special interrelationship of the two detection species with the remaining assay components that result when forming a particular detection complex

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is not a necessary technical feature in the present case as defined in PCT Article 6 and PCT Rule 13.